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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/302,434	04/30/1999	KLAUS BOSSLET	026083/0119	6895

26633 7590 10/01/2002

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/01/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/302,434	BOSSLET ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-43,47,49 and 51-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-43,47,49 and 51-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 10, 2002 has been entered.

2. Claims 37-43, 47, 49, and 51-58 are pending and examined on the merits.

Claim Rejections Withdrawn:

3. The rejection of claims 37-58 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn, upon further consideration.

New Grounds of Rejection:

4. Claims 37-43, 47, 49, and 51-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39, dependent from claim 37, recites the limitation that the carbohydrate residue is a lactose. There is insufficient antecedent basis for this limitation in claim 37, which recites that the carbohydrate residue may be, among other carbohydrates, N-acetyllactose.

Claims 37, 54 and 58 "said glycoprotein". Claims 37 and 58 refer to a "fusion glycoprotein".

Claim 57 is indefinite because it is confusing. Claim 57 is drawn to a kit further comprising galactose, which is a compound that would affect the clearance of a galactosylated bifunctional fusion glycoprotein or conjugate. However, claim 57 depends from claim 37 that excludes additional components that affect clearance of bifunctional fusion glycoproteins or conjugates.

5. Claims 37-43, 47, 49, and 51-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that claims 37-58 introduce new matter into the specification. Claims 37-58 were not originally filed with the specification or with any of the parents. Claims 37-58 recite that the claimed kits lack an additional component that affects clearance of the first component. The specification does not support the breadth of this negative limitation. The specification only describes methods and compounds and kits where an additional component that affects clearance either by administration of the clearance compound either simultaneously or after the administration of first and second components. The specification does not describe a method that excludes the use of an agent that affects clearance, where the agent is administered prior to the administration of the first and second components. The specification also only describes one example of a clearance-affecting compound that is to be excluded from the claimed kits, the example of an

antibody that binds to the bifunctional fusion glycoproteins or conjugates. This example is not representative of the many compounds that may affect clearance of the bifunctional fusion glycoproteins and conjugates. Furthermore, evidence that applicants did not intend to exclude any clearance-affecting compound is that the specification contemplates the admixture of galactose with the bifunctional fusion glycoprotein or conjugate, so that galactose would be administered simultaneously with the bifunctional fusion glycoprotein or conjugate (page 10, lines 1-5). The addition of galactose would affect the clearance rate of a galactosylated bifunctional fusion glycoprotein or conjugate.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 37, 38, 40-43, 47, 49, 52, 54-55 and 58 are rejected under 35 U.S.C. 102(e) as being anticipated by Bagshawe (U.S. 5,632,990, issued May 27, 1997; effective filing date Dec. 21, 1990).

Claims 37, 38, 40-43, 47, 49, 52 and 54-55 are drawn to pharmaceutical kits comprising a first component and a second component. The first component comprises a bifunctional fusion glycoprotein or conjugate, comprising at least one first portion, which is an enzyme that is penicillin G amidase, penicillin V amidase, β-lactamase, alkaline phosphatase, carboxypeptidase G2, carboxypeptidase A, cytosine deaminase, nitroreductase, diaphorase, arylsulfatase, glycosidase, β-glucosidase, or β-glucuronidase; and at least one second portion, which comprises a monoclonal antibody or antigen binding fragment thereof that binds a first component to a tumor-specific antigen on a tumor cell, wherein the first component comprises at least one carbohydrate complement comprising at least one exposed carbohydrate residue that is mannose, galactose, N-acetylglucosamine, N-acetyllactose, glucose, or fucose. The second component comprises a non-toxic prodrug that is cleaved into a tumor cytotoxic drug by said enzymatic activity of the first component. The pharmaceutical kit lacks an additional component that affects clearance of said first component. Each of the first and second components is in a pharmaceutically acceptable vehicle. Claims 40-43 recite product-by-process limitations for the carbohydrate residue present in the first component, which do not appear to materially change the chemical nature of the carbohydrate residue. Claim 47 limits the tumor specific antigen to a tumor associated antigen selected from a list that includes CEA. Claims 54 and 55 recite that the glycoprotein portion or the conjugate portion of the fusion glycoprotein or conjugate may be

synthesized in mammalian host cells, microorganisms, insect cell and transgenic animals. The mammalian cell may be a CHO cell. These limitations are considered product-by-process limiations that do not materially affect the chemical nature of the fusion glycoproteins or conjugates. Claim 56 adds the limitation that the kit further comprises an agent capable of lowering the pH in a tumor to be treated. Claim 57 adds the limitation that the kit further comprises galactose. Claim 58 is a method of treating a tumor in a subject, comprising administering a bifunctional fusion glycoprotein or conjugate that is the same as that of claim 37.

Claims 37 and 58 recite that the kits and methods lack an additional component that affects clearance. As noted in the rejection of the claims under 35 U.S.C. 112, first paragraph, for introduction of new matter, the specification only teaches that an additional component that affects clearance will not be added simultaneously or subsequently to the administration of the claimed bifunctional fusion glycoproteins or conjugates. For the purposes of this rejection, the claims will be interpreted as set forth in the specification, that the additional component that is lacking is a component that will be administered either simultaneously or after the administration of the fusion glycoprotein or glycoconjugate.

Bagshawe claims conjugates and fusion proteins and two-component systems, and discloses methods of treatment using the conjugates, fusion proteins or two-component systems, comprising antibody A5B7 (binds CEA tumor associated antigen) linked to an enzyme that is either carboxypeptidase G2 or nitroreductase, and administering a prodrug. Bagshawe discloses that the antibody-enzyme conjugate may be modified by the addition of additional galactose or other sugar residues (col. 4, line 19-38). It is noted that Bagshawe teaches the administration of

a clearance-affecting agent, asialofetuin. However, the asialofetuin is administered prior to the administration of the conjugate.

Bagshawe teaches that the antibody may be a monoclonal antibody or a humanized antibody (col. 2, line 32- col. 3, line 32). Bagshawe teaches that the antibody portion and the enzyme portion may be joined by conjugation or a recombinant fusion protein. The conjugation may be via a linking component (col. 2, lines 32-46). The fusion protein may be produced by eukaryotic or prokaryotic cells (col. 2, line 38-46).

Thus, Bagshawe discloses fusion glycoproteins or conjugates that are the same as that claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 37-43, 47, 49, 52, 54, 55 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Senter (U.S. 4,975,278; issued Dec. 4, 1990) in view of Mattes (Mattes, M.J., Journal of the National Cancer Institute, 79(4): 855, 1987; cited in IDS).

Senter discloses conjugates and fusion proteins comprising an enzyme portion and an antibody portion for targeting the enzyme to a tumor cell. Senter discloses methods comprising administering the conjugates or fusion proteins and then administering a prodrug that is converted by the enzyme portion of the conjugate or fusion protein into a cytotoxic compound. Senter discloses that the antibody portion may target the p97 tumor antigen (col. 16, lines 6-17). Senter discloses that the enzyme portion may be alkaline phosphatase, arylsulfatase, cytosine deaminase, β-lactamase, penicillin V amidase, pencillin G amidase (col. 9, lines 13-33). Senter discloses that the antibody portion may be a monoclonal antibody, a humanized antibody or an antibody fragment (col. 8. lines 31-65). Senter discloses that the linkage between enzyme and antibody may be chemical linkages via crosslinking agents, or that enzyme and antibody may be bound together as a fusion protein (col. 9., line 59- col. 10, line10).

Senter fails to disclose or teach that the antibody enzyme conjugate or fusion protein may comprise at least one exposed carbohydrate residue that is either a mannose, galactose, N-acetylglucosamine, N-acetyllactose, glucose or fucose.

However, Mattes teaches that antibodies may be galactosylated to increase their clearance from the blood (page 858 – 860). Mattes teaches that increased clearance from the blood of antibodies is desirable in order to reduce reactivity of the monoclonal antibodies in areas away from the tumor (in this case outside of the peritoneal cavity). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have

combined the teachings of Senter with that of Mattes to alter the antibody-enzyme conjugates or fusion proteins of Senter by the addition of a galactose so that the antibody-enzyme conjugates or fusion proteins are more rapidly cleared from the blood. One would have been motivated to modify the conjugates or fusion proteins of Senter in order to increase the relative tumor to blood ratio, which would be achieved if antibody-enyzme conjugates or fusion proteins are rapidly cleared from the blood.

8. Claims 37-43, 47, 49, 52, 54, 55 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Senter (U.S. 4,975,278; issued Dec. 4, 1990) in view of Mattes (Mattes, M.J., Journal of the National Cancer Institute, 79(4): 855, 1987; cited in IDS), and further in view of Steer (Steer, C.L. and Ashwell, G., Progress in Liver Diseases, VIII: 99, 1986; cited in the IDS).

The teachings of Senter and Mattes is discussed above in section #7. Mattes teaches the desirability of galactosylating an antibody. However, the claimed bifunction fusion proteins and conjugates may also comprise mannose, N-acetylglucosamine or fucose. Steer teaches that the liver contains receptors that recognize and bind glycoproteins with exposed N-aceytlglucosamine, mannose or fucose residues (page 99-100, also entire document). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used sugars such as mannose, N-acetylgucosamine or fucose to increase the clearance of bifunctional fusion glycoproteins or conjugates from the blood.

9. Claims 37, 49, 51, 53 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (EP 501,215; published Feb. 9, 1992; cited in the IDS; German language) as

evidenced by Derwent database English language abstract; in view of Mattes (Mattes, M.J., Journal of the National Cancer Institute, 79(4): 855, 1987; cited in IDS).

Claims 37, 49, 51-53 and 58 are examined to the extent they read on kits and methods of use, comprising bifunctional fusion glycoproteins or conjugates where the monoclonal antibody is BW431/26 or where the first component comprises the formula huTuMab-L-β-gluc, wherein huTuMab is a human tumor specific monoclonal antibody or an antigen binding fragment thereof, L is a linker molecule and β-gluc is a human β-glucuronidase.

Seemann teaches bifunctional fusion glycoproteins comprising antigen binding fragments of the BW431/26 antibody and teaches a fusion protein of the formula huTuMab-L-β-gluc. Seeman also teaches that this fusion protein may be used to target β-glucuronidase to tumors via the antibody component, and teaches that chemical modification may improve half-life and tumor localization (from Derwent database English language abstract). Seemann fails to teach galactosylation. However, Mattes teaches that antibodies may be galactosylated to increase their clearance from the blood (page 858 – 860). Mattes teaches that increased clearance from the blood of antibodies is desirable in order to reduce reactivity of the monoclonal antibodies in areas away from the tumor (in this case outside of the peritoneal cavity). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Seemann with that of Mattes to alter fusion proteins of Seemann by the addition of a galactose so that the fusion proteins are more rapidly cleared from the blood. One would have been motivated to modify the fusion proteins of Seemann in order to increase the relative tumor to blood ratio, which would be achieved if antibody-enyzme conjugates or fusion proteins are rapidly cleared from the blood.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
September 28, 2002

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